ACTA
STOMATOLOGICA
CROATICA
www.ascro.hr

Acta stomatol Croat. 2019;53(3):363-370.
DOI: 10.15644/asc53/4/7

ORIGINAL SCIENTIFIC PAPER
IZVORNI ZNANSTVENI RAD

Ana Družijanić[1], Ana Glavina[1], Mirna Draganja[2], Dolores Biočina-Lukenda[1,3], Livia Cigić[3,4]

Inflammatory Markers and Incidence of other Autoimmune Diseases in Patients with Oral Lichen Planus

Upalni markeri i učestalost drugih autoimunih bolesti u oboljelih od oralnoga lihena planusa

[1] Dental Clinic Split, Croatia
Stomatološka poliklinika Split, Hrvatska
[2] Student of Study program of Dental Medicine, School of Medicine University of Split, Croatia
Studentica 5. godine Studija dentalne medicine Medicinskog fakulteta Sveučilišta u Splitu, Hrvatska
[3] Department of Oral medicine and Periodontology, University of Split School of Medicine, Split, Croatia
Studij dentalne medicine Medicinskog fakulteta Sveučilišta u Splitu – Odjel za maksilofacijalnu kirurgiju KBC-a Split, Hrvatska
[4] University Hospital of Split, Croatia
Klinički bolnički centar Split, Hrvatska

Abstract

Introduction: Oral lichen planus (OLP) is a chronic immune, inflammatory disease of the oral cavity of a still unknown etiology. **Materials and methods:** The study involved 63 subjects diagnosed with oral lichen planus and 63 subjects without pathologic changes in the oral mucosa who were classified as controls. All subjects were given a detailed medical history at first screening. The medical history of the presence of other autoimmune disease in all subjects was supported by medical records. A sample of venous blood was taken from each subject in order to determine sedimentation rate (SE) and leukocyte count (L) using standard laboratory procedures, and serum C-reactive protein (CRP) concentration values were determined as well. **Statistical analysis:** The methods of descriptive statistics, χ2-test, the Fisher's exact test, and the Student's t-test were used in the statistical processing of the results. The results were interpreted at a significance level of P <0.05. **Results:** For all three measured inflammatory markers, there were no statistically significant differences in the number of subjects with elevated values between the test and control groups (P = 0.364 for SE; P = 1.000 for CRP and P = 0.219 for L). The prevalence of other autoimmune disease in the OLP group was higher than in the control group, with statistical significance, and the most common was cutaneous lichen in nine subjects (14.29%) with OLP and celiac disease seven subjects (11.11%). **Conclusions:** The results showed that there was no significant difference in the average values of the investigated inflammatory markers in blood (SE, CRP and L) between patients with OLP and control subjects, while a significantly higher incidence of other autoimmune diseases in patients with OLP was demonstrated.

Received: October 30, 2019
Accepted: December 1, 2019

Address for correspondence
Assistant professor Livia Cigić, DMD, PhD
School of Medicine University of Split
University Hospital of Split
Šoltanska 2, 21000 Split, Croatia
Tel. +38521557845
livia.cigic@mefst.hr

Key words
Oral Lichen Planus; Autoimmune Disease; Inflammation; C-Reactive Protein

Introduction

Oral lichen planus (OLP) is a chronic immunological, inflammatory disease of the oral mucosa, of still unknown etiology. Cell-mediated immunity triggered by endogenous and exogenous factors holds a special place in the pathogenesis of OLP, especially in individuals with a genetic predisposition to disease. The disease may occur along with skin changes, in case of which it is referred to as skin lichen planus (LP). Oral changes can occur at the same time as skin lesions, but in 30 to 70% of cases they occur separately (1). LP has been associated with a number of autoimmune disorders, but it remains unclear whether patients with LP are more likely to develop other autoimmune diseases or the diseases are related etiologically (2). Cutaneous LP may also occur in some autoimmune diseases, such as Sjögren's syndrome (SS), rheumatoid arthritis (RA), sarcoidosis, autoimmune hepatitis and vitiligo

Uvod

Oralni lihen planus (OLP) kronična je imunosna upalna bolest sluznice usne šupljine još nerazjašnjene etiologije. Stanično posredovana imunost potaknuta endogenim i egzogenim utjecajima zauzima posebno mjesto u patogenezi OLP-a i to osobito ako osoba ima genetsku predispoziciju za nastanak bolesti. Bolest se može pojavljivati udruženo s kožnim promjenama te se u tom slučaju govori o kožnom lihenu planusu (LP-u). Oralne promjene mogu se pojavljivati istodobno s kožnim lezijama, ali se u čak 30 do 70 % slučajeva pojavljuju zasebno (1). LP se dovodi u vezu s nizom autoimunih poremećaja, ali ostaje nejasno jesu li bolesnici s LP-om podložniji razvoju drugih autoimunih bolesti ili su one povezane etiološki (2). Kožni LP može se pojaviti i u sklopu nekih autoimunih bolesti kao što su Sjögrenov sindrom (SS), reumatoidni artritis (RA), sarkoidoza, autoimuni hepatitis i vitiligo

(3). The occurrence of OLP can also be enhanced by psychological distress, stress and anxiety (4).

Pathogenetic mechanisms of OLP formation imply an autoimmune reaction in which T lymphocytes invade antigenically altered basal keratinocytes. The target antigen that triggers the reaction has not yet been detected. In susceptible patients, basal keratinocytes present antigen permanently, leading to chronicity and their direct cell-mediated damage (5). The inflammatory infiltrate in OLP is composed of lymphocytes and a small number of macrophages. T lymphocytes dominate over B lymphocytes, and CD4 + T (helper) cells are more common than CD8 + T cells (cytotoxic / suppressor) (6).Autoimmune disease (AID) is a pathological condition triggered by an autoimmune process (7). The etiology of AID is multifaceted. It is caused by impaired neuroendocrine - humoral regulation of immunity in genetically predisposed individuals exposed to the provocative action of external factors. Epidemiological studies have shown that genetic factors determine the preference for AID, as indicated by family relatedness and more frequent diseases of identical and fraternal twins. According to Roitt, organ specific diseases are distinguished from a wide range of AIDs versus organ nonspecific or multisystemic diseases (8).

The importance of the autoimmune reaction in the etiopathogenesis of OLP is based on studies that have observed some changes in the population of T lymphocytes in the peripheral blood of patients, including decreased CD4 + and CD45RA + lymphocytes. The finding of suppressed spontaneous lymphocyte proliferation in peripheral blood mediated by CD4 + and CD45RA + cells indicates their importance in the onset of this disease (3). Oral lichen planus can be associated with AIDs and disorders with CD4 + and CD45RA + cell reduction (3). The association of chronic liver disease with the onset of OLP has also been noted, especially autoimmune liver diseases such as primary biliary cirrhosis (PBC) and chronic active hepatitis (9, 10). Diabetes mellitus (DM) is often described as an important etiologic factor in OLP formation (11). A possible etiological background of ulcerative colitis in the onset of OLP has also been described (12, 13). Among other intestinal diseases, celiac disease (14) and Chron's disease (15) are associated with OLP. A more common occurrence of OLP has also been reported in patients with some skin diseases such as psoriasis or lichen sclerosus (3).

Previous studies have shown significant increase in inflammatory markers levels in OLP patients (16). Moreover, it is concluded that plasma CRP level could be a potential marker of increased risk of cancer (17).

The main objectives of this study were: 1) to investigate differences in the values of the inflammatory markers (sedimentation (SE), C-reactive protein (CRP), leukocytes (L)) between subjects with OLP and subjects without pathological changes in the oral mucosa; 2) examine differences in the incidence of the disease from other autoimmune diseases between subjects with OLP and healthy subjects of the control group.

(3). Nastanku OLP-u mogu pogodovati i psihičke smetnje, stres i anksioznost (4).

Patogenetski mehanizmi nastanka OLP-a podrazumijevaju autoimunu reakciju u kojoj T-limfociti napadaju antigeno promijenjene bazalne keratinocite. Ciljni antigen koji pokreće reakciju još nije otkriven. Kod podložnih bolesnika bazalni keratinociti trajno prezentiraju antigen, što dovodi do kroniciteta i njihova izravnog stanično posredovanog oštećenja (5). Upalni infiltrat u OLP-u sastavljen je od limfocita i manjeg broja makrofaga. T-limfociti dominiraju u odnosu prema B-limfocitima, a CD4+T-stanice (pomoćničke) češće su negoli CD8+T-stanice (citotoksično/supresorske) (6).

Autoimuna bolest (AIB) patološko je stanje potaknuto autoimunim procesom (7). Etiologiju AIB-a uvjetuje više čimbenika. Nastaje zbog poremećene neuroendokrinohumoralne regulacije imunosti kod genetski predisponiranih osoba izloženih provokacijskom djelovanju vanjskih čimbenika. U epidemiološkim studijama ističe se da genetski čimbenici determiniraju sklonost prema AIB-u, na što upućuje obiteljska povezanost i češće obolijevanje jednojajčanih i dvojajčanih blizanaca. Prema Roittu, iz širokoga spektra AIB-a izdvajaju se organospecifične bolesti nasuprot organonespecifičnim, odnosno multisustavnim bolestima (8).

Važnost autoimune reakcije u etiopatogenezi OLP-a temelji se na istraživanjima u kojima su se opazile promjene u populaciji T-limfocita u perifernoj krvi oboljelih, uključujući smanjeni broj limfocita CD4+ i CD45RA+. Nalaz suprimirane spontane proliferacije limfocita u perifernoj krvi posredovan stanicama CD4+ i CD45RA+ upućuje na njihovu važnost u nastanku te bolesti (3). Oralni lihen planus može se povezati s mnogim AIB-ima i poremećajima kod kojih je uočena redukcija stanica CD4+ i CD45RA+ (3). Uočena je i povezanost kroničnih bolesti jetre s pojavom OLP-a, posebno autoimunih jetrenih bolesti poput primarne bilijarne ciroze (PBC-a) i kroničnog aktivnog hepatitisa (9, 10). Diabetes mellitus (DM) često se opisuje kao važan etiološki čimbenik u nastanku OLP-a (11). Također je opisana moguća etiološka pozadina ulceroznoga kolitisa. (12, 13). Od ostalih crijevnih bolesti, u vezu s OLP-om dovode se celijakija (14) i Chronova bolest (15). Češća pojava OLP-a opisana je i kod oboljelih od nekih kožnih bolesti kao što su psorijaza ili lihen sklerosus (3).

U dosadašnjim studijama istaknuto je značajno povećanje upalnih markera kod pacijenata s oralnim lihenom (16). Štoviše, zaključeno je da razina CRP- a u plazmi može biti pokazatelj povećanog rizika od razvoja karcinoma (17).

Glavni ciljevi ovog istraživanja bili su:

1) ispitati postoji li razlika u vrijednostima ispitivanih upalnih markera (sedimentacije – SE-a, reaktivnog C-proteina – CRP-a i leukocita – L-a) između ispitanika s OLP-om i onih bez patoloških promjena na sluznici usne šupljine

2) ispitati postoji li razlika u učestalosti i drugih autoimunih bolesti između ispitanika s OLP-om i zdravih ispitanika iz kontrolne skupine.

Materials and methods

Respondents and Procedures

The study was initiated with the approval of the Ethics Committee of the University of Split, School of Medicine. It was implemented according to the principles of the Declaration of Helsinki in the period from September 2011 to July 2017. Respondents were included in the survey after signing inform consent. A total of 126 subjects participated in the study. The study group consisted of 63 subjects who were diagnosed with OLP by clinical oral examination and histopathological findings. The control group consisted of 63 randomly selected subjects with no pathological changes in the oral mucosa.

From all subjects a detailed medical history was taken during the first examination at the Department of the Oral Medicine of the Dental Polyclinic Split - Teaching Database Study of Dental Medicine, School of Medicine, University of Split. Based on the medical history, data were obtained on age, sex, cigarette smoking habits (yes / no) and daily consumption of alcoholic beverages (yes / no), and the presence of other autoimmune diseases. The medical history of the presence of another autoimmune disease is supported by detailed medical records. Pathohistological diagnosis (PHD) confirmed the clinically diagnosed OLP. A biopsy specimen for PHD was taken from the edge of a pathologically altered oral mucosa after application of a local anesthetic (0.7 ml). The histopathological criteria of OLP included the following: hyperkeratosis and various stages of orthokeratosis or parakeratosis, vacuolation of the basal layer with apoptotic keratinocytes, dense lymphocytic inflammatory cell infiltrate at the epithelial-connective border, presence of eosinophilic colloidal body bodies in the area of basal lamina (Civatte bodies) and epithelial lengthening (appearance of saw teeth). The erosive forms of OLP histopathologically have included the presence of erosion, neutrophils and fibrin deposits in the epithelium. All subjects in the test group were in the acute phase of the disease at the time of taking part in the study and their blood was taken for analysis before treatment was initiated.

The exclusion criterion for the test group was an acute febrile condition, and the subjects were asked about it before engaging in blood research and sampling.

Laboratory analysis

All serological examinations were performed in the same laboratory of the Institute for Medical-Biochemical Diagnostics of the Clinical Hospital Center Split. A sample of venous blood was taken from each patient to determine SE rate and L number using standard laboratory procedures. CRP concentration was determined after blood sampling in a Vacutainer tube without anticoagulants (Becton Dickinson, Plymouth, UK). Multigent CRP Vario reagent was used for the determination of CRP on an ARCHITECT ci8200 (Abbot, Wiesbaden, Germany) following the manufacturer's instructions. The serological findings of SE, CRP and L are expressed metrically, in defined units and with defined reference values: SE (5-28 mm / h), CRP (<5.0 mg / L) and L

Materijali i metodologija

Ispitanici i postupci

Istraživanje je počelo nakon odobrenja Etičkog povjerenstva Medicinskog fakulteta Sveučilišta u Splitu. Provedeno je prema načelima Helsinške deklaracije od rujna 2011. do srpnja 2017. godine. Ispitanici su uključeni u istraživanje nakon što su potpisali informirani pristanak. Sudjelovalo ih je ukupno 126. Ispitnu skupinu činila su 63 ispitanika kojima je kliničkim oralnim pregledom i patohistološkim nalazom potvrđena dijagnoza OLP-a, a u kontrolnoj su bila 63 nasumično odabrana ispitanika bez patoloških promjena na oralnoj sluznici.

Svim ispitanicima uzeta je detaljna anamneza tijekom prvog pregleda u ambulanti Odjela za oralnu medicinu Stomatološke poliklinike Split – nastavne baze Studija dentalne medicine Medicinskog fakulteta Sveučilišta u Splitu. Na temelju anamneze dobiveni su podatci o dobi, spolu, navikama svakodnevnog pušenja cigareta (da/ne) i svakodnevnog konzumiranja alkoholnih pića (da/ne) te o drugim autoimunim bolestima. Anamnestički podatci o prisutnosti druge autoimune bolesti potkrijepljeni su detaljnom medicinskom dokumentacijom. Patohistološkom dijagnostikom (PHD-om) potvrđena je klinički postavljena dijagnoza OLP-a. Biopsijski uzorak za PHD uzet je s ruba patološki promijenjene oralne sluznice nakon apliciranja lokalnog anestetika (0,7 ml). Histopatološki kriteriji OLP-a uključivali su sljedeće: hiperkeratozu i različite stupnjeve ortokeratoze ili parakeratoze, vakuolizaciju bazalnog sloja s apoptotičnim keratinocitima, gusti limfocitni upalni stanični infiltrat na epitelno-vezivnoj granici, eozinofilna koloidna tjelešca u području bazalne membrane (Civatte bodies) i nazupčani izgled epitelnih produljaka (izgled poput zubaca pile). Erozivni oblici OLP-a uključivali su patohistološki i erozije, neutrofile i fibrinske depozite u epitelu. Isključni kriterij bile su displazije u lezijama OLP-a.

Svi iz ispitne skupine bili su u akutnoj fazi bolesti kada su uključeni u istraživanje te im je izvađena venska krv za analizu prije nego što su počeli s liječenjem.

Kriterij za isključenje za ispitnu skupinu bilo je akutno febrilno stanje, o čemu su ispitanici odgovorili prije uključivanja u istraživanje i uzorkovanja krvi.

Laboratorijske analize

Sve serološke pretrage provedene su u istom laboratoriju Zavoda za medicinsko-biokemijsku dijagnostiku Kliničkoga bolničkog centra Split. Svakom bolesniku izvađen je uzorak venske krvi za određivanje brzine sedimentacije i broja leukocita standardnim laboratorijskim postupcima. Određivanje vrijednosti koncentracije CRP-a obavljalo se nakon uzimanja uzorka krvi u Vacutainer tubu bez antikoagulansa (Becton Dickinson, Plymouth, Velika Britanija). Za određivanje CRP-a upotrijebljen je reagens Multigent CRP Vario na uređaju ARCHITECT ci8200 (Abbot, Wiesbaden, Njemačka), a prema priloženim uputama proizvođača. Serološki nalazi sedimentacije, C-reaktivnog proteina i leukocita izraženi su metrički, u definiranim jedinicama i s definiranim referen-

(3,4-9, 7 x 109 / L). The values of SE, CRP, and L are also presented qualitatively; as values within the reference interval (negative) or values greater than the upper limit of the reference interval (elevated).

Statistical analysis

The collected data were entered into spreadsheets and an analysis was performed using the statistical package Statistica 12. In the statistical processing of the results, the methods of descriptive statistics, $\chi 2$-test, Fisher's exact test, and the Student's t-test were used. The values of the continuous variables are presented by the mean and the median, and the categorical variables are presented as an integer and a percentage. A $\chi 2$ test was used to compare the categorical variables between the test and control groups. Due to the limitations of the $\chi 2$ test when applied in situations where the presence of the feature modality is low, Fisher's exact test was used. T-test tested the difference in numerical values among the observed groups. The results were interpreted at a significance level of $P < 0.05$.

Results

A total of 126 subjects participated in the study, 23 men and 103 women. The test group consisted of 54 women (85.71%) and 9 men (14.29%), while in the control group there were 49 women (77.78%) and 14 men (22.22%). There was no statistically significant difference among the study groups with respect to the gender of the subjects (P = 0.248).

Table 1 shows the mean, median and minimum and maximum age of the test and control subjects.

tnim vrijednostima: SE (5 – 28 mm/h), CRP (< 5,0 mg/L) i L (3,4 – 9,7 x 109/L). Vrijednosti SE-a, CRP-a i L-a prikazane su i kvalitativno; kao vrijednosti unutar referentnog intervala (negativne) ili vrijednosti više od gornje granice referentnog intervala (povišene).

Statistička analiza

Prikupljeni podatci uneseni su u proračunske tablice te su analizirani statističkim paketom Statistica 12. U statističkoj obradi rezultata korištene su metode deskriptivne statistike, $\chi 2$-test, Fisherov egzaktni test te Studentov t-test. Vrijednosti kontinuiranih varijabli prikazane su srednjom vrijednošću i medijanom, a kategorijske varijable kao cijeli broj i postotak. Za usporedbu kategorijskih varijabli između ispitne i kontrolne skupine korišten je $\chi 2$-test. Zbog ograničenja koja ima $\chi 2$-test pri primjeni u situacijama male zastupljenosti modaliteta obilježja, primijenjen je Fisherov egzaktni test. T-testom ispitala se razlika u numeričkim vrijednostima među promatranim skupinama. Rezultati su interpretirani na razini značajnosti $P < 0,05$.

Rezultati

U istraživanju je sudjelovalo ukupno 126 ispitanika – 23 muškarca i 103 žene. Ispitnu skupinu činile su 54 žene (85,71 %) i 9 muškaraca (14,29 %), a u kontrolnoj skupini bilo je 49 žena (77,78 %) i 14 muškaraca (22,22 %). Među ispitivanim skupinama nije bilo statistički značajne razlike s obzirom na spol ispitanika ($P = 0,248$).

U tablici 1. prikazane su srednje vrijednosti, medijan te minimalna i maksimalna dob ispitanika za ispitnu i kontrolnu skupinu.

Table 1. Age structure of respondents
Tablica 1. Dobna struktura ispitanika

Variable • Varijabla	Group • Skupina	Statistical Parameters • Statistički parametri				
		N	X	M	Minimum	maximum
AGE • DOB	OLP	63	62.62	62	40	80
	Control group • Kontrolna skupina	63	62.21	64	40	81

OLP - oral lichen planus • oralni lihen planus, N – number of participants • broj ispitanika, X – mean value • srednja vrijednost, M – median • medijan

There was no statistically significant difference between the study groups with respect to the age of the subjects (P = 0.819).

The average value of SE in subjects with OLP was 12.17 mm / h, whereas in the control group it was 12.36 mm / h. No statistically significant difference in mean SE was found between the study groups (P = 0.902). The average CRP value in subjects with OLP was 3.56 mg / L and in the control group was 2.45 mg / L (P = 0.270). The average value of L was 5.84 x 109 / L in the test group and 6.01 x 109 / L in the control group (P = 0.575).

Table 2 shows the proportion of subjects whose values of test inflammatory markers (SE, CRP, L) were elevated (above the upper limit of the reference interval).

Između ispitivanih skupina nije bilo statistički značajne razlike s obzirom na dob ispitanika (P = 0,819).

Prosječna vrijednost SE-a kod ispitanika s OLP-om bila je 12,17 mm/h, a u kontrolnoj skupini iznosila je 12,36 mm/h. Nije utvrđena statistički značajna razlika u srednjoj vrijednosti sedimentacije između ispitivanih skupina (P = 0,902). Prosječna vrijednost CRP-a kod ispitanika s OLP-om bila je 3,56 mg/L, a u kontrolnoj skupini 2,45 mg/L (P = 0,270). Prosječna vrijednost L-a iznosila je 5,84 x 109/L u ispitnoj skupini, te 6,01 x 109/L u kontrolnoj (P = 0,575).

U tablici 2. prikazan je udio ispitanika čije su vrijednosti ispitivanih upalnih markera (SE-a, CRP-a, L-a) bile povišene (iznad gornje granice referentnog intervala).

Table 2 Proportion of subjects whose inflammatory marker values were elevated
Tablica 2. Udio ispitanika čije su vrijednosti upalnih markera bile povišene

	SE N (%)	CRP N (%)	L N (%)
OLP	14 (22.22%)	7 (11.11%)	8 (12.70%)
Control group • Kontrolna skupina	10 (15.87%)	7 (11.11%)	2 (3.17%)

OLP- oral lichen planus • oralni lihen planus, SE- sedimentation • sedimentacija, CRP- C reactive protein • C-reaktivni protein, L- leukocytes • leukociti
Values are expressed as an integer and a percentage • vrijednosti su izražene kao cijeli broj i postotak.

For all three measured inflammatory markers, there was no statistically significant difference in the number of subjects with elevated values between the test and control groups (P = 0.364 for SE; P = 1.000 for CRP and P = 0.219 for L).

Table 3 shows the proportion of subjects diagnosed with another autoimmune disease in both study groups.

Za sva tri mjerena upalna markera nije bilo statistički značajne razlike u broju ispitanika s povišenim vrijednostima između ispitne i kontrolne skupine (*P* = 0,364 za SE; *P* = 1,000 za CRP i *P* = 0,219 za L).

U tablici 3. prikazan je udio ispitanika koji imaju dijagnosticiranu neku drugu autoimunu bolest u objema ispitivanim skupinama.

Table 3 Proportion of subjects with other autoimmune disease
Tablica 3. Udio ispitanika s drugom autoimunom bolešću

	OTHER AUTOIMUNE DISEASE • DRUGA AUTOIMUNA BOLEST		
	YES • DA N (%)	NO • NE N (%)	P
OLP	25 (39.68 %)	38 (60.32 %)	<0,001
Control group • Kontrolna skupina	4 (6.35 %)	59 (93.65 %)	

OLP- oral lichen planus • oralni lihen planus
Values are expressed as an integer and a percentage • vrijednosti su izražene kao cijeli broj i postotak

Nine subjects (14.29%) with OLP has reported the presence of cutaneous LP, seven (11.11%) celiac disease, five (7.94%) DM, three subjects (4.76%) SS and one respondent (1.59%) indicated the existence of Hashimoto's thyroiditis, RA and vitiligo. In the control group of autoimmune diseases, SS was reported in two subjects (3.17%) and DM and Raynaud's syndrome in one subject (1.59%).

Anamnestic data on daily basis consumption of cigarettes and alcohol were taken. In the test group, seven subjects (11.11%) smoke every day while 11 (17.46%) consume alcoholic beverages every day. In the control group, 11 subjects (17.46%) have reported smoking cigarettes every day, and seven (11.11%) alcohol consumption. There was no statistically significant difference between smoking and drinking (P = 0.308) and drinking (P = 0.308) between the study groups.

Devet ispitanika (14,29 %) s OLP-om navelo je kožni LP, sedam (11,11 %) celijakiju, pet (7,94 %) DM, tri (4,76 %) SS, a jedan je ispitanik (1,59 %) naveo Hashimotov tireoiditis, RA i vitiligo. U kontrolnoj skupini od autoimunih bolesti navode se SS kod dva ispitanika (3,17 %) te DM i Raynaudov sindrom kod jednoga (1,59 %).

Anamnestički su uzeti podatci o navikama svakodnevnog konzumiranja cigareta i alkohola. U ispitnoj skupini sedam ispitanika (11,11 %) puši svaki dan, a 11 (17,46 %) svakodnevno konzumira alkoholna pića. U kontrolnoj skupini 11 ispitanika (17,46 %) navelo je da svaki dan puši cigarete, a sedam (11,11 %) pije alkohol. Između ispitivanih skupina nije bilo statistički značajne razlike u navikama pušenja (*P* = 0,308) i konzumiranja alkoholnih pića (*P* = 0,308).

Discussion

Oral lichen planus is an inflammatory disease of the oral cavity mucosa (18), hence the aim of this study was to investigate whether there was a difference in the values of inflammatory markers (SE, CRP, and L) between the patients with OLP and subjects without pathological changes in the oral mucosa .

Determination of the rate of SE is a laboratory test which determines the presence of an inflammatory reaction in the body. Measurement demonstrates a change in plasma protein concentration, and changes in plasma composition will cause accelerated SE (30). The average value of SE in subjects with OLP was 12.17 mm / h and in the control group was 12.36

Rasprava

Oralni lihen planus upalna je bolest sluznice usne šupljine (18) i zato je cilj ovog istraživanja bio ispitati postoji li razlika u vrijednostima upalnih markera (SE-a, CRP-a i L-a) između oboljelih od OLP-a i ispitanika bez patoloških promjena na oralnoj sluznici.

Određivanje brzine SE-a laboratorijski je test kojim se utvrđuje upalna reakcija u organizmu. Mjerenjem se dokazuje promjena koncentracije plazmatskih bjelančevina, a promjene u sastavu plazme uzrokovat će ubrzanu sedimentaciju (30). Prosječna vrijednost SE-a kod ispitanika s OLP-om iznosila je 12,17 mm/h, a u kontrolnoj skupini 12,36 mm/h, što nije bilo statistički značajno različito (*P* = 0,902). Ipak,

mm / h, which was not significantly different (P = 0.902). Nevertheless, a slightly larger number of OLP subjects than those in the control group (14 vs. 10) had increased sedimentation (> 28 mm / h).

Protein synthesis is accelerated in response to inflammation in liver cells the most important of which is CRP. Plasma CRP concentration correlates best with SE value (19). In their study, Shahidi et al. demonstrated a significant increase in CRP levels in subjects with dysplastic OLP lesions and oral squamous cell carcinoma (16). In this study, we did not include subjects with dysplastic OLP lesions as this was the exclusive criterion. In both study groups, 56 subjects (88.89%) had CRP values lower than 5 mg / L, respectively, i.e. within the reference interval. The average CRP value in subjects with OLP was 3.56 mg / L, while in the control group it was 2.45 mg / L which, although lower, was not statistically significant (P = 0.270).

Leukocytosis is a common reaction of the body to bacterial inflammation (17). The average L value was 5.84 x 109 / L in the test group and 6.01 x 109 / L in the control group, which also showed no statistically significant difference (P = 0.575). Five subjects (7.94%) with OLP and two subjects (3.17%) in the control group had the increased value L (> 9.7 x 109 / L). In our study, we did not prove a statistically significant difference in the values of inflammatory markers (SE, CRP, and L) in the blood between subjects with OLP and the subjects without pathological changes in the oral cavity mucosa.

The importance of the autoimmune reaction in the etiopathogenesis of OLP is based on studies in which changes in T lymphocyte populations in peripheral blood of patients have been noted (20). In this study, 25 subjects (39.68%) with OLP reported a history of another autoimmune disease, whereas in the control group, only four (6.35%) reported a history of another autoimmune disease, which is a statistically significant difference (P <0.001). A study by Cigić et al showed a higher incidence of celiac disease in patients with OLP than in people with healthy oral mucosa and among the ordinary population (21). This fact is confirmed by the results of our study because celiac disease was the second most common autoimmune disease in subjects with OLP.

Every day cigarette smoking and alcohol consumption did not show statistically significant differences between the study groups. Although these habits are not directly related to the development of OLP, changes in similar clinical and histopathological appearance can sometimes be caused by the toxic effect of alcohol and cigarettes on oral mucosa. Barbosa et al. do not link OLP with these habits in their research (20). Most OLP patients were non-smokers (97.3%) and they did not consume alcohol (20), as shown by our study.

Conclusion

Although no statistically significant difference in the mean values of the examined inflammatory markers in blood (SE, CRP, L) between OLP patients and control subjects was found in this study, there was a statistically significantly higher incidence of other autoimmune diseases in patients with

povišenu sedimentaciju (> 28 mm/h) imalo je nešto više ispitanika s OLP-om, negoli onih iz kontrolne skupine (14 vs 10).

Kao odgovor na upalu u jetrenim se stanicama ubrzava sinteza bjelančevina, a najvažniji od njih jest CRP. Koncentracija CRP-a u plazmi najbolje korelira s vrijednošću SE-a (19). Shahidi i suradnici u svojem su istraživanju dokazali značajan porast razine CRP-a kod ispitanika s displastičnim lezijama OLP-a i oralnim karcinomom pločastih stanica (16). U ovom istraživanju nismo uključili ispitanike s displastičnim lezijama OLP-a jer je to bio isključni kriterij. U obje ispitivane skupine po 56 ispitanika (88,89 %) imalo je vrijednost CRP-a manju od 5 mg/L, odnosno unutar referentnog intervala. Prosječna vrijednost CRP-a kod ispitanika s OLP-om iznosila je 3,56 mg/L, a u kontrolnoj skupini bila je 2,45 mg/L što, iako niže, nije bilo statistički značajno (P = 0,270).

Leukocitoza je uobičajena reakcija tijela na bakterijske upale (17). Prosječna vrijednost leukocita iznosila je 5,84 x 109/L u ispitnoj skupini i 6,01 x 109/L u kontrolnoj, što također nije pokazivalo statistički značajnu razliku (P = 0,575). Povišenu vrijednost L-a (> 9,7 x 109/L) imalo je pet ispitanika (7,94 %) s OLP-om i dva (3,17 %) iz kontrolne skupine. U našem istraživanju nismo dokazali statistički značajnu razliku u vrijednostima upalnih markera (SE-a, CRP-a i L-a) u krvi između ispitanika s OLP-om i onih bez patoloških promjena na sluznici usne šupljine.

Važnost autoimune reakcije u etiopatogenezi OLP-a temelji se na istraživanjima u kojima su opažene promjene u populaciji T-limfocita u perifernoj krvi oboljelih (20). U ovom istraživanju 25 ispitanika s OLP-om (39,68 %) anamnestički navodi i drugu autoimunu bolest, a u kontrolnoj skupini to navodi samo njih četvero (6,35 %), što je statistički značajna razlika (P < 0,001). Istraživanje L. Cigić i njezinih suradnika pokazalo je veću učestalost celijakije kod oboljelih od OLP-a u odnosu prema osobama sa zdravom sluznicom usne šupljine i u usporedbi s općom populacijom (21). To potvrđuju i rezultati našeg istraživanja jer je celijakija bila druga najčešća autoimuna bolest kod ispitanika s OLP-om.

Navike svakodnevnog pušenja cigareta i konzumiranja alkoholnih pića nisu pokazale statistički značajne razlike među ispitivanim skupinama. Iako se spomenute navike ne dovode izravno u vezu s razvojem OLP-a, promjene sličnoga kliničkog i patohistološkog izgleda katkad mogu biti uzrokovane toksičnim učinkom alkohola i cigareta na oralnu sluznicu. Barbosa i suradnici u svojem istraživanju ne povezuju OLP i navedene navike (20). Većina bolesnika s OLP-om bili su nepušači (97,3 %) te nisu konzumirali alkohol (20), što je pokazalo i naše istraživanje.

Zaključak

Iako se u ovom istraživanju nije pokazala statistički značajna razlika u prosječnim vrijednostima ispitivanih upalnih markera u krvi (S-a, CRP-a, L-a) između oboljelih od OLP-a i ispitanika iz kontrolne skupine, postojala je statistički značajno veća učestalost drugih autoimunih bolesti kod oboljе-

OLP- a, the most common of which were cutaneous LP and celiac disease. The statistically significantly higher incidence of other autoimmune diseases in patients with OLP indicates the importance of exclusion of these diseases during the diagnostic process, but also a possible common etiopathogenetic mechanism that needs to be investigated and confirmed by further studies. There was no statistically significant difference between the study groups in daily consumption of cigarettes and alcoholic beverages. This shows that smoking and alcohol are not etiologic factors but factors that contribute to the deterioration of the clinical picture of OLP, therefore, smoking and alcohol consumption habits are not recommended for patients with OLP. Future OLP research should focus on the autoimmune mechanisms of this disease.

Conflict of interest

The authors were in no conflict of interest.

Appendix

The results of this research were presented at the 3rd Congress of the Croatian Society of Oral Medicine and Pathology held on October 16-17, 2018. in Zagreb.

lih od OLP-a, a najčešće su bile kožni LP i celijakija. Statistički značajno veća pojavnost drugih autoimunih bolesti kod oboljelih od OLP-a upućuje na važnost isključenja tih bolesti tijekom dijagnostičkog procesa, ali i na mogući zajednički etiopatogenetski mehanizam koji je potrebno istražiti i potvrditi u budućim studijama. Nije bilo statistički značajne razlike među ispitivanim skupinama u navikama svakodnevnog uživanja cigareta i alkoholnih pića. To pokazuje da pušenje i alkohol nisu etiološki čimbenici, nego pridonose pogoršanju kliničke slike OLP-a, pa se pušenje i konzumacija alkohola ne preporučuju bolesnicima s OLP-om. Buduća istraživanja OLP-a treba usmjeriti na autoimune mehanizme u nastanku te bolesti.

Sukob interesa

Autori nisu bili ni u kakvom sukobu interesa.

Dodatak

Rezultati ovog istraživanja prezentirani su na 3. kongresu Hrvatskog društva za Oralnu medicinu i patologiju održanog 16. - 17. 10. 2018. u Zagrebu.

Sažetak

Uvod: Oralni lihen planus (OLP) kronična je imunosna upalna bolest sluznice usne šupljine još nerazjašnjene etiologije. **Materijali i metode:** U istraživanju su sudjelovala 63 ispitanika s dijagnozom oralnoga lihena planusa i 63 bez patoloških promjena na oralnoj sluznici – oni su svrstani u kontrolnu skupinu. Svim ispitanicima uzeti su anamnestički podatci o prisutnosti druge autoimune bolesti te im je izvađen uzorak venske krvi za određivanje brzine sedimentacije (SE-a), broja leukocita (L-a) i koncentracije C-reaktivnog proteina u serumu (CRP-a). **Statistička analiza:** U statističkoj obradi korištene su metode deskriptivne statistike, $\chi 2$-test , Fisherov egzaktni test te Studentov t-test. Rezultati su interpretirani na razini značajnosti $P < 0,05$. **Rezultati:** Za sva tri mjerena upalna markera nije bilo statistički značajne razlike u broju ispitanika s povišenim vrijednostima između ispitne i kontrolne skupine ($P = 0,364$ za SE; $P = 1,000$ za CRP i $P = 0,219$ za L). Promatrajući druge autoimune bolesti, statistički je značajno bila veća učestalost u ispitnoj skupini, a najčešće su to bili kožni lihen kod devet ispitanika (14,29 %) i celijakija kod sedam (11,11%). **Zaključci:** Rezultati su pokazali da nema značajne razlike u prosječnim vrijednostima ispitivanih upalnih markera u krvi između oboljelih od OLP-a i ispitanika u kontrolnoj skupini te je dokazana značajno veća učestalost drugih autoimunih bolesti kod oboljelih od OLP-a, najčešće kožni lihen i celijakija.

Zaprimljen: 30. listopada 2019.
Prihvaćen: 1. prosinca 2019.

Adresa za dopisivanje
doc. dr. sc. Livia Cigić
Sveučilište u Splitu
Medicinski fakultet
Katedra za oralnu medicinu i parodontologiju
Šoltanska 2, 21 000 Split, Hrvatska
tel: +38521557845
livia.cigic@mefst.hr

Ključne riječi
oralni lihen planus; autoimuna bolest; upala; C-reaktivna bjelančevina

References

1. Canjuga I, Mravak- Stipetić M, Lončar B, Kern J. The Prevalence of Systemic Diseases and Medications in Patients with Oral Lichen Planus. Acta Stomatol Croat. 2010;44(2):96-100.
2. Shuttleworth D, Graham-Brown RAC, Campbell AC. The autoimmune background in lichen planus. Br J Dermatol. 1986 Aug;115(2):199-203.
3. Biočina-Lukenda D. Oralni lihen ruber I. Etiologija i patogeneza. Acta Stomatol Croat. 2002;36:451-73.
4. Gavic L, Cigic L, Biocina-Lukenda D, Gruden V, Gruden Pokupec JS. The role of anxiety, depression, and psychological stress on the clinical status of recurrent aphthous stomatitis and oral lichen planus. J Oral Pathol Med. 2014 Jul;43(6):410-7.
5. Greenberg, MS; Glick, M - editors. Burketova oralna medicina: dijagnoza i liječenje. 10 th ed. Zagreb: Medicinska naklada; 2006.
6. Rodrígez-Núñez I, Blanco-Carrión A, García AG, Rey JG. Peripheral T-cell subsets in patients with reticular and atrophic – erosive oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001 Feb;91(2):180-8.
7. Gamulin, S; Marušić, M; Kovač Z - editors. Patofiziologija. 7 th ed. Zagreb: Medicinska naklada; 2011.
8. Roitt IM, De Carvalho LC. The immunological basis of autoimmune disease. Ciba Found Symp. 1982;(90):22-34.
9. Powell FC, Rogers RS, Dickson ER. Primary biliary cirrhosis and lichen planus. J Am Acad Dermatol. 1983 Oct;9(4):540-5.
10. Lodi G, Pellicano R, Carrozzo M. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. Oral Dis. 2010 Oct;16(7):601-12.
11. Lundström J. Incidence of diabetes mellitus in patients with oral lichen planus. Int J Oral Surg 1983;12:147-52.
12. GISED (Gruppo Italiano Studi Epidemiologici in Dermatologia). Epidemiological evidence of the association between lichen planus and two immune-related diseases: Alopecia areata and ulcerative colitis. Arch Dermatol 1991;127:688-91.
13. Dhawan SS, Fields K. Lichen planus and ulcerative colitis; is there a relationship? Int J Dermatol. 1989 Oct;28(8):534.
14. Fortune F, Buchanan JA. Oral lichen planus and coeliac disease. Lancet. 1993 May 1;341(8853):1154-5.
15. Kano Y, Shiohara T, Yagita A, Nagashima M. Erythema nodosum, lichen planus and lichen nitidus in Chron's disease: report of case and analysis of T cell receptor V gene expression in the cutaneous and intestinal lesions. Dermatology. 1995;190(1):59-63.
16. Shahidi M, Jafari S, Barati M, Mahdipour M, Gholami MS. Predictive value of Salivary microRNA-320a, vascular endothelial growth factor receptor 2, CRP and IL-6 in Oral lichen planus pro-

gression. Inflammopharmacology 2017; doi: 10.1007/s10787-017-0352-1. [Epub ahead of print].
17. Vankadara SK, Balmuri PK. Evaluation of Serum C-Reactive Protein Levels in Oral Premalignancies and Malignancies: A Comparative Study. J Dent (Tehran). 2018;15:358-64.
18. Scully C, el-Kom M. Lichen planus: review and update on pathogenesis. J Oral Pathol. 1985 Jul;14(6):431-58.
19. Damjanov, I; Seiwerth, S; Jukić, S; Nola, - editors. Patologija. 4th ed. Zagreb: Medicinska naklada; 2014.
20. Barbosa NG, Silveira EJ, Lima EN, Oliveira PT, Soares MS, de Medeiros AM. Factors associated with clinical characteristics and symptoms in a case series of oral lichen planus. Int J Dermatol. 2015 Jan;54(1):e1-6.
21. Cigic L, Gavic L, Simunic M, Ardalic Z, Biocina-Lukenda D. Increased prevalence of celiac disease in patiens with oral lichen planus. Clin Oral Investig. 2015 Apr;19(3):627-35.